66. (Amended) The immunologically isolated stromal cells of claim 37, wherein said immunologically isolated stromal cells are cultured for about three to about thirty days.

67. (Amended) The immunologically isolated stromal cells of claim 37, wherein said immunologically isolated stromal cells are cultured for about five to about fourteen days.

68. (Amended) The immunologically isolated stromal cells of claim 37, wherein said immunologically isolated stromal cells are cultured for about seven to about ten days.

REMARKS

The present invention relates to novel isolated stromal cells and methods of using the cells in treatment of a variety of human diseases, disorders or conditions. The invention discloses methods comprising administering isolated stromal cells into a human patient thereby effecting treatment of a disease, disorder or condition in the human. Moreover, the stromal cells can be cultured *in vitro*, genetically engineered to produce therapeutic compounds, or both, prior to administration into the human.

Claims 37, 38, and 55-68 are pending in the application. Claims 1-36 and 39-44 were previously withdrawn by the Examiner as being drawn to a non-elected invention.

Claims 37, 38, and 56-58, and 65-68, have been amended to more particularly point out and distinctly claim the subject matter which Applicant regards as his invention. Support for these amendments is found in the specification as filed as more fully set forth below. Thus, no new matter has been added by way of these amendments.

Rejection of Claims 37, 38, and 55-68, Under 35 U.S.C. § 112, second paragraph

Claims 37, 38, and 55-68 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully submit that these claims are not indefinite in any way. As more fully set forth below, Applicants respectfully submit

that they have clearly defined the terms objected to by the Examiner as Applicants are entitled to do under present patent law.

It is settled law that the "patent law allows the inventor to be his own lexicographer." *Chicago Steel Foundry Co. v. Burnside Steel Foundry Co.*, 132 F.2d 812 (7th Cir. 1943). *See also* MPEP § 2173.01. This is because "[t]he dictionary does not always keep abreast of the inventor. It cannot. Things are not made for the sake of words, but words for things." *Autogiro Co. v. U.S.*, 155 USPQ 697 (Ct. Cls. 1967). Further, applicant is entitled to have the claims construed in connection with the other parts of the application. *See Autogiro Co. v. U.S.*, 155 USPQ 697 (Ct. Cls. 1967); *see also Miles Labs., Inc. v. Shandon, Inc.*, 27 USPQ2d 1123 (Fed. Cir. 1993), *cert. denied*, 510 U.S. 1100 (1994) (reiterating that claims must "have a clear and definite meaning when construed in the light of the complete patent document") (emphasis added). Therefore, Applicants are entitled to define terms to describe their invention and the claims must be interpreted in light of the other parts of the application including the disclosure in the specification and the definitions provided therein.

Applicants respectfully submit that when claims 37, 38, and 55-68 are interpreted in light of the disclosure of the specification and the definitions set forth therein, it is clear that these claims are in no way vague and indefinite.

The Examiner contends that claim 37, and 38, and 55-68, depending therefrom, are rendered vague and indefinite by reciting the term "immunologically isolated stromal cells." That is, in the Examiner's view, it is unclear whether the term means cells isolated from the organism and thus isolated from the immune system; cells isolated using antibody; or cells encapsulated such that they are not in contact with cells of the immune system. The Examiner further contends that it is unclear whether the cells are *in vitro* or *in vivo* (Office Action at page 3).

Applicants do not understand the Examiner's apparent confusion as to the meaning of the term "immunologically isolated" as it relates to their invention. Applicants respectfully point out that the disclosure provided in the specification makes it abundantly clear what the term "immunologically isolated" means. More specifically, the specification from page 6, line 24, to page 7, line 3, sets forth an extensive definition of the term:

> As used herein, "immunologically isolated", "immunologically protected", "immunologically neutralized", and "a manner that physically isolates them from the recipient's immune system" are meant to refer to the encapsulation, containment or other physical separation of an implanted cell from the body into which it is implanted such that the cell is not exposed to and cannot be eliminated by the immune system of the body such that cells which are immunologically isolated are administered in a manner that physically isolates them from the recipient's immune system. Examples of immunological isolation means include, but are not limited by, well known technologies and devices such as microencapsulation, biocompatible matrices, diffusion chambers, implantable cartridges, implant devices with membrane assemblies and other containers with membranes. It is preferred that cells are immunologically isolated by maintaining them with implant devices. (Emphasis added).

Therefore, the specification makes clear that the cells referred to as "immunologically isolated" are implanted cells present in the body of a recipient and are physically isolated from the recipient's immune system. Thus, cells that are merely removed from an organism, without more, are not the "immunologically isolated" cells of Applicants' invention since they are not implanted. Furthermore, cells that are removed from a body and kept in, for instance, a petri dish, are not present in a body of a recipient and are not physically isolated from a recipient's immune system since there is, obviously, no recipient!

With regard to the Examiner's query as to whether the cells are isolated using an antibody, one skilled in the art would understand, based upon the disclosure provided in the specification as filed, that cells may be selected using an antibody and then implanted into the body of a recipient. Such cells may be "immunologically isolated," as defined by Applicants, if they are also physically separated from the immune system of the recipient once the cells are located within the recipient's body. Therefore, how the cells are selected, *e.g.*, using antibody selection, is not a limitation of the present invention; rather, what is important for purposes of the invention is that the cells, once inside the body of a recipient, are not exposed to and cannot be eliminated by the immune system of the recipient. Only then are the cells

"immunologically isolated" as defined by Applicants and as made clear by the definition at pages 6-7 of the specification and as exemplified therein.

Therefore, the term "immunologically isolated" is defined clearly by Applicants in the specification as filed to mean cells that are implanted into a recipient and are physically separated from the recipient's immune system. Thus, cells that are simply removed from a body, without being inserted into a recipient, cannot be "immunologically isolated" as defined by Applicants, and the specification as filed makes it abundantly clear that this strained reading of the phrase is not intended by Applicants.

The Examiner further contends that claims 37 and 56 are vague and indefinite in that it is unclear what is meant by a "beneficial" protein. That is, the Examiner contends that "beneficial" is a relative term and that it is unclear whether the protein is beneficial for a host cell or a host organism or what the benefits of such a protein are.

Applicants respectfully point out that the term "beneficial protein" is defined in the specification and is exemplified therein and the term is not vague and indefinite in any way. More specifically, "beneficial protein" is defined in the specification at page 7, lines 4-13:

> As used herein, "beneficial protein" and "heterologous protein" are interchangeable and are meant to refer to 1) proteins which can compensate for the protein encoded by defective genes and/or insufficient gene expression that is causally linked to the disease or symptoms in diseases, disorders or conditions characterized by a gene defect and 2) proteins whose presence alleviates, reduces, prevents or causes to be alleviated, reduced or prevented, the causes and/or symptoms that characterize diseases, disorders and conditions which can be treated with beneficial proteins.

In addition to this clear definition of the term, Applicants, at page 15, lines 13-23 of the specification, have set forth an extensive, albeit partial, list of some of the diseases, disorders or conditions that can be treated by administering immunologically isolated stromal cells expressing a beneficial protein, *e.g.*, growth hormone deficiency, diabetes, adenine daemons deficiency, hemophilia, α_1-antitrypsin

deficiency, Fabray disease, familial hypercholesterolemia, Gaucher's disease, Lesch-Nyhan Syndrome, Maple syrup urine disease, ornithine transcarbamylase deficiency, phenylketonuria, Sandhoff disease, Tay-Sachs disease, and von Willebrand disease. Therefore, one skilled in the art would understand, based upon the disclosure provided in the specification, the beneficial protein that can be used to treat these diseases. This is sufficient under 35 U.S.C. §112, second paragraph, since the knowledge of the skilled artisan informs the inquiry as to whether a claim is vague and indefinite. More specifically, it is well-settled that "whether a claim is invalid under [Section 112, second paragraph,] requires a determination whether those skilled in the art would understand what is claimed." *Bausch & Lomb, Inc. v. Alcon Labs., Inc.*, 52 USPQ2d 1385, 1387 (W.D.N.Y. 1999) (citing *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1217, 18 USPQ2d 1016, 1030 (Fed. Cir. 1991). Thus, based upon the disclosure provided in the specification, the skilled artisan would not be confused as to what "beneficial protein" is encompassed in the invention and the claims are not vague and indefinite under 35 U.S.C. §112, second paragraph.

Even assuming, *arguendo*, that the skilled artisan would not appreciate, based upon the disclosure provided of the diseases, disorders or conditions that can be treated by providing a "beneficial protein", what the term meant, the skilled artisan would certainly not find the term vague and indefinite given the extensive list of "beneficial proteins" provided in the specification. That is, the specification, at page 16, lines 21-30, and at Tables IV and V (at the far right column), disclose a variety of "beneficial proteins," including, but not limited to: growth hormone, Ob protein, erythroprotein, proteins involved in insulin synthesis and regulated release, Apo-A1, estrogen agonist specific for bone cells, antibodies to infectious agents, glutaminase, adenine deaminase, lipoprotein lipase, acid β-glucosidase, α-antitrypsin, four enzymes involved in galactosemia, Factor VIII, Factor IX, granulocyte-macrophage colony stimulating factor, granulocyte colony stimulating factor, interleukin-2, and interleukin-1 receptor antagonist protein. In addition, "beneficial proteins," as the term is used in the specification, are exemplified in Example 1 (collagen 1), and Examples 3-5 (human growth hormone, human obesity protein, and human factor IX).

As pointed out previously elsewhere herein, the Examiner contends that "beneficial" is a relative term and is, therefore, vague. Applicants respectfully point out that relative terms are not *per se* vague or proscribed under the present patent law. Recently, in *Bausch & Lomb, Inc. v. Alcon Labs., Inc.*, 52 USPQ2d 1385 (W.D.N.Y. 1999), the District Court for the Western District of New York, found that the relative term "substantially inhibit" did not render the claims in a patent vague *per se* although the term might require comparative analysis. The *Bausch & Lomb* Court reviewed the current law with respect to relative terms of degree as follows:

> The law is clear that the use of terms of degree, such as "substantially," in patent claims does not necessarily render the claims indefinite. In fact, the Court of Appeals for the Federal Circuit has recognized that such "words are ubiquitous in patent claims." Therefore, "[t]hat some claim language may not be precise . . . does not automatically render a claim invalid." *Bausch & Lomb, Inc.*, 52 USPQ2d at 1391-92 (citations omitted).

Therefore, reciting a relative term does not necessarily render the claims vague and indefinite under 35 U.S.C. §112, second paragraph. Instead, the *Bausch & Lomb* Court pointed out that the analysis for determining whether a relative term is vague and indefinite has been set out by the Court of Appeals for the Federal Circuit:

> A decision as to whether a claim is invalid under [Section 112 Para. 2] requires a determination whether those skilled in the art would understand what is claimed. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1217, 18 USPQ2d 1016 (Fed. Cir.) (citing *Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 758 F.2d 613, 624, 225 USPQ 634 (Fed. Cir.) (claims must "reasonably apprise those skilled in the art" as to their scope and be "as precise as the subject matter permits"), *cert. denied*, 474 U.S. 976 (1985), *cert. denied*, 502 U.S. 856 (1991)). The degree of precision with which the claims must be stated to meet the definiteness requirement "is a function of the nature of the subject matter." *Miles Labs., Inc. v. Shandon, Inc.*, 997 F.2d 870, 875, 27 USPQ2d 1123 (Fed. Cir. 1993), *cert. denied*, 510 U.S. 1100 (1994). Thus, "[t]he amount of detail required to be included in claims depends on the particular invention and prior art, and is not to be viewed in the abstract . . .," but in conjunction with the specifications of the patent.

> *Shatterproof Glass*, 758 F.2d at 624. Accordingly, "[t]hat some claim language may not be precise . . . does not automatically render a claim invalid. When a word of degree is used the district court must determine whether the patent's specification provides some standard for measuring that degree," such that a person of ordinary skill in the art would understand what is claimed. *Seattle Box Co. v. Industrial Crating & Packing, Inc.*, 731 F.2d 818, 826, 221 USPQ 568 (Fed. Cir. 1984). In addition, "[m]athematical precision should not be imposed for its own sake; a patentee has the right to claim the invention in terms that would be understood by persons of skill in the field of the invention." *Modine Mfg. Co. v. United States Int'l Trade Comm'n*, 75 F.3d 1545, 1557, 37 USPQ2d 1609 (Fed. Cir.), *cert. denied*, 518 U.S. 1005 (1996). *Bausch & Lomb*, 52 USPQ2d at 1387.

As the above passage explains, whether a relative term renders a claim vague and indefinite is determined in light of the disclosure provided in the specification and with regard to what one of ordinary skill in the art would understand. As pointed out previously elsewhere herein, the term "beneficial protein" is clearly defined in the specification. Further, the specification provides numerous examples of diseases, disorders or conditions that can be treated by administering a beneficial protein. Indeed, the application discloses an extensive list of beneficial proteins that are encompassed by the invention. Given this extensive disclosure, one of ordinary skill in the art would understand what is claimed by claims reciting the term "beneficial protein." Thus, this term is not vague and indefinite under 35 U.S.C. §112, second paragraph, irrespective of whether this is a relative term or not.

For the reasons set forth previously herein, the phrase "immunologically isolated" is not vague and indefinite in any way and claims 37, 38, and 55-68, are not vague and indefinite under 35 U.S.C. §112, second paragraph, for reciting the phrase. Therefore, Applicants respectfully request that the rejection of these claims be reconsidered and withdrawn.

The Examiner also contends that claims 37, 38, and 57, are vague and indefinite in reciting the phrase "said stromal cells" in that there is no antecedent basis for that phrase, but there antecedent basis for the phrase "said immunologically isolated

stromal cells" or "the cells." While not necessarily agreeing with the Examiner, Applicants, in a good faith effort to expedite prosecution of this application, have amended claims 37, 38, and 57, to recite "said immunologically isolated stromal cells" instead of "said stromal cells." This amendment merely relates the term "said stromal cells" to the proper antecedent basis, *i.e.*, to "immunologically isolated stromal cells." Thus, no new matter has been added by way of this amendment.

Since claims 37, 38, and 57, as amended, are not vague and indefinite, the rejection of these claims under 35 U.S.C. §112, second paragraph, should be reconsidered and withdrawn.

The Examiner contends that claim 56 is rendered vague and indefinite by the term "an obesity factor" because it is unclear whether the obesity factor is leptin or some other obesity-related protein. While not necessarily agreeing with the Examiner, Applicants, in a good faith effort to expedite the prosecution of this application, have amended claim 56 to recite that the beneficial protein is selected from the group consisting of, *inter alia*, Obesity protein. Support for this amendment is found at, among other places, page 16, lines 21-27; page 27, line 27; page 36, lines 15-23; page 37, line 36, to page 38, line 1. Therefore, no new matter has been added by way of this amendment.

Amendment of claim 56 to recite "Obesity protein" instead of "obesity factor" renders the rejection of this claim under 35 U.S.C. §112, second paragraph, moot. That is, the disclosure provided in the specification makes clear that the Obesity protein, which term is used interchangeably with "obesity factor" throughout the specification, means the product of the OB gene as described in, *e.g.*, Considine et al. (1995, J. Clin. Invest. 95:2986-2988) (*see*, *e.g.*, specification at page 16, lines 21-27; page 37, line 36, to page 38, line 1). Thus, one of ordinary skill in the art, armed with the disclosure provided in the specification as filed, would not be confused as to what is meant by "Obesity protein." Therefore, claim 56, as amended, is not vague and indefinite under 35 U.S.C. §112, second paragraph, and the rejection of this claim should be reconsidered and withdrawn.

The Examiner further contends that claims 58 and 65-68 are rendered vague and indefinite by the phrase "said cells" since there is no proper antecedent basis

for the phrase. Applicants, while not necessarily agreeing with the Examiner that there is no proper antecedent basis for the term "said cells," have amended the claims to recite "said immunologically isolated stromal cells" instead of "said cells" in a good faith effort to expedite prosecution of this application. No new matter has been added by way of this amendment which merely recites the full phrase "immunologically isolated stromal cells" whenever these cells, which are the antecedent basis of the term, are mentioned in the claims.

Claims 58 and 65-68, as amended, are not vague and indefinite under 35 U.S.C. §112, second paragraph, since there is proper antecedent basis for the phrase "said immunologically isolated stromal cells" as now recited therein. Therefore, the rejection of these claims should be reconsidered and withdrawn.

The Examiner also contends that claim 58 is vague and indefinite in that it is unclear what is meant by the term "matched donor stromal cells." More specifically, in the Examiner's view, it is unclear to what the donor stromal cells are matched. Applicants respectfully submit that the term "matched donor" is a well-known term of art in the art of transplantation such that the skilled artisan would understand what is meant by the term and would not be confused thereby. Therefore, the term "matched donor" is not vague and indefinite since the term would be understood by persons of skill in the field of the invention. *See Modine Mfg. Co.*, 75 F.3d at 1557.

Moreover, the specification makes clear that a "matched donor" refers to "a normal, matched syngeneic donor" at page 8, lines 22-23, which is the first mention of the term in the detailed description of the invention. Further, the specification provides a specific example of a "matched donor" in that the specification discloses that matched donor cells in Example 1 were obtained from mice "from the same inbred FVB/N line" as the recipient mice. Thus, the disclosure in the specification as filed makes clear that "matched donor" indicates a syngeneic donor that is matched to the recipient organism. Moreover, this is a well-known term of art and the skilled artisan would not be confused thereby in the light of the complete patent document. Therefore, the term "matched donor" is not vague and indefinite under 35 U.S.C. §112,

second paragraph, and the rejection of this claim should be reconsidered and withdrawn.

The Examiner contends that claim 62 is rendered vague and indefinite by the term "a second gene" since it is unclear how the construct is structured. More specifically, the Examiner contends that it is unclear whether the second gene is in tandem with the first gene or whether the second gene is flanked by regulatory elements which are distinct from the first gene. Applicants respectfully submit that claim 62 is not vague and indefinite in any way.

As stated previously elsewhere herein, the standard for whether a claim is vague and indefinite under 35 U.S.C. §112, second paragraph, is whether those skilled in the art would understand what is claimed, *i.e.*, whether the claim reasonably apprises those skilled in the art as to its scope. Further, the claims are to be construed in light of the other parts of the specification.

Applicants respectfully submit that under the present patent law, claim 62 reasonably apprises those skilled in the art as to its scope because the skilled artisan would understand, based upon the disclosure provided in the specification as filed, that the crucial feature of the "second gene" is that it be co-expressed in the cell that also expresses the first gene, *i.e.*, the gene encoding the beneficial protein. One skilled in the art would appreciate, based upon the disclosure provided in the specification, that whether the second gene is tandem with respect to the first gene or whether it is flanked by regulatory elements which are distinct from those flanking the first gene is irrelevant for purposes of the present invention. Further, the specification indicates that the second gene need not even be present within the same construct so long as both genes are expressed within the same cell (specification at page 19, line 35, to page 20, line 25). Indeed, the specification states:

> A second gene is usually co-transfected or linked to the therapeutic gene. The second gene is frequently a selectable antibiotic-resistance gene. Transfected cells can be selected by growing the cells in an antibiotic that will kill cells that do not take up the selectable gene. In most cases where the two genes are unlinked and co-transfected, the cells that survive the antibiotic treatment have both genes in them and express both of them (specification at page 21, lines 30-37).

Therefore, the specification makes clear that although the first and second genes can be present within the same construct, the genes need not be provided to a cell in a single construct. Nevertheless, the specification makes clear that the invention also encompasses a construct comprising the second gene (*e.g.*, the lacZ gene, neomycin resistance gene, thymidine kinase gene) together with the first gene (specification at Examples 3-5; Figure 1) in a single construct. Indeed, a preferred construct is depicted in Figure 1 which illustrates a construct comprising a first (neomycin resistance) gene and a second (lacZ) gene placed in tandem in a retrovirus vector where each gene is operably linked to a separate promoter/regulatory sequence. The specification teaches that the lacZ gene can be easily replaced with a gene encoding a beneficial protein (*i.e.*, the hGH gene, the OB gene, and the human factor IX gene) (specification at page 37, line 35, to page 38, line 2) using a construct such as that depicted in Figure 1. The skilled artisan would understand, based upon the disclosure provided in the specification, that the invention is not limited to any particular construct design; rather, the skilled artisan would understand that the invention includes a wide variety of construct designs wherein the first and second genes, and regulatory elements operably linked thereto, are arranged in various permutations well-known in the art. Therefore, one skilled in the art, based upon the disclosure provided in the specification, would not be confused by the term "second gene" where the skilled artisan would understand that the precise design of the construct comprising the first and second gene is not essential to the present invention which encompasses a variety of construct designs well-known in the art of recombinant technology.

Therefore, claim 62, is not vague and indefinite for purposes of 35 U.S.C. §112, second paragraph, and the rejection of this claim should be reconsidered and withdrawn.

The Examiner further contends that claim 59 is vague and indefinite because, in the Examiner's opinion, the claim indicates that only one regulatory element is required while the specification discloses that "the regulatory elements necessary for gene expression include: a promoter, an initiation codon, a stop codon, and a polyadenylation signal. It is necessary that these elements be operable in the

stromal cells or in cells that arise from the stromal cells after infusion into an individual" (Office Action at page 4 *citing* specification at page 17, lines 27-31). The Examiner contends that it is unclear whether a construct containing only one regulatory element is expressible.

Applicants respectfully submit that claim 59 is not vague and indefinite under 35 U.S.C. §112, second paragraph. The Examiner contends that although claim 59 is not vague and indefinite in and of itself, it is indefinite because the claim apparently conflicts with a statement made in the specification at page 17, lines 27-31. However, the specification does not conflict with the claims since the statement that "[t]he regulatory elements necessary for gene expression include: a promoter, an initiation codon, a stop codon, and a polyadenylation signal" does not mean that each of the listed elements must be present in the construct. Rather, the statement simply means that the listed elements are included among the various regulatory elements well-known in the art and/or disclosed in the specification. That is, the statement merely sets forth a list, which includes, but is not limited to, regulatory elements encompassed by the invention. The statement merely makes clear that other elements which are not explicitly listed are nevertheless encompassed in the invention. A plain reading of the statement demonstrates that the statement only means that the list is not to be considered exhaustive. There is nothing to suggest that each and every element must be included in each gene construct of the invention since the sentence simply states that regulatory elements include those listed.

Further, this would not have been the understanding of one skilled in the art based upon the disclosure provided in the specification. That is, it was well-known in the art at the time the specification was filed that there are genes that, for example, do not require a promoter for expression and that certain genes do not contain a polyadenylation sequence and encode mRNA which does not comprise a polyadenylation sequence. Thus, the skilled artisan, armed with the teachings of the invention, would not be confused by a sentence that lists regulatory elements well-known in the art, which can be operably linked to a gene encoding a beneficial protein as disclosed in the specification.

In addition, the statement that "[i]t is necessary that these elements be operable in the stromal cells or in cells that arise from the stromal cells after infusion into an individual" is not vague and indefinite. This is because the skilled artisan, based upon the disclosure provided in the specification, would appreciate that the statement merely indicates that if a regulatory element is included in the construct, the regulatory element must be operable once the cell is infused into a recipient. One skilled in the art would understand, based upon the disclosure provided in the specification, that expression of a beneficial protein by the isolated stromal cells of the invention is a crucial feature of the invention such that driving expression of the protein in a cell is a requisite. Indeed, the specification goes on to state:

> Initiation codons and stop codons are generally considered to be part of a nucleotide sequence that encodes the protein. However, it is necessary that these elements are functional in the stromal cells or cells that arise from stromal cells. Similarly, promoters and polyadenylation signals used must be functional within the stromal cells or cells that arise from stromal cells (specification at page 17, line 35, to page 18, line 4).

Thus, the passage quoted by the Examiner merely makes clear that any regulatory element included in the construct must be operably linked to the nucleic acid encoding the beneficial protein and drive its expression. Further, one skilled in the art, armed with the disclosure provided in the specification, would understand that not all regulatory elements listed are necessary for successful expression of a beneficial protein and that the list provided is not intended to be exhaustive to the skilled artisan. Therefore, claim 59 is not vague and indefinite when construed in light of the other parts of the application and the rejection under 35 U.S.C. §112, second paragraph, should be reconsidered and withdrawn.

For the reasons set forth above, claims 37, 38, and 55-68 are not vague and indefinite under 35 U.S.C. § 112, second paragraph, and the rejection of these claims on that basis should be reconsidered and withdrawn.

Rejection of Claims 37, 38, and 55-68, Under 35 U.S.C. § 102(e)

Claims 37, 38, 55, and 57-68 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Cerami et al. (U.S. Patent No. 5,846,796, issued on December 8,

1998, with an effective filing date of February 26, 1993). The Examiner contends that Cerami et al. teach a population of isolated mesenchymal cells which are removed from the body and are, therefore, immunologically isolated. Having found that the cells are immunologically isolated, the Examiner then contends that Cerami et al. teach each and every single claim limitation. Applicants respectfully submit that Cerami et al. cannot anticipate the claims under 35 U.S.C. §102(e).

It is well settled that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP §2131 (quoting *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). "The identical invention must be shown in as complete detail as is contained in the . . . claim." *Id.* (quoting *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Therefore, Cerami et al., must describe each and every element of claim 37, 38, 55, and 57-68, in order to anticipate these claims under Section 102(b).

Applicants respectfully submit that Cerami et al., does not teach each and every element of the claims 37, 38, and 55-68, and Cerami et al., cannot therefore anticipate these claims. More specifically, as discussed previously elsewhere herein, merely removing a stromal cell from an organism does not render such cell "immunologically isolated" as that term is described by Applicants. This is because, as more fully set forth elsewhere herein, the "immunologically isolated" stromal cells must be implanted cells present in the body of a recipient that are physically isolated from the recipient's immune system. Clearly, the cells taught by Cerami et al., which are merely removed from the body and are not transplanted into a recipient, and where the cells are not present within the body of a recipient where they are physically separated from the recipient's immune system, cannot be not the cells of Applicants' invention. Thus, Cerami et al., do not teach each and every element as set forth in claims 37, 38, and 55-68, and cannot anticipate these claims. Therefore, the rejection of these claims under 35 U.S.C. §102(e) should be reconsidered and withdrawn.

Rejection of Claims 37, 57-60, and 65-68, Under 35 U.S.C. § 102(b)

Claims 37, 57-60, and 65-68 stand rejected under 35 U.S.C. §102(b) as being anticipated by Carter et al. (1992, Blood 79:356-364). Once again, the Examiner

contends that Carter et al. teach isolated stromal cells which are immunologically isolated since they are removed from the body. Applicants submit that Carter et al. cannot anticipate the cells of claim 37, 57-60, and 65-68, because merely removing cells from a body does not render the cells "immunologically isolated" as recited in the claims. As discussed previously elsewhere herein with regard to Cerami et al., Applicants respectfully submit that merely removing cells from a body and placing them in culture does not render the cells "immunologically isolated" as the term is defined by Applicants. Therefore, Carter et al. does not teach each and every single claim limitation and cannot anticipate the claims under 35 U.S.C. §102(e), and the rejection of the claims should be reconsidered and withdrawn.

Rejection of Claims 37, 58-61, and 65-68, Under 35 U.S.C. § 102(a)

Claims 37, 58-61, and 65-68, stand rejected under 35 U.S.C. §102(a) as being anticipated by Pereira et al. (1995, Proc. Natl. Acad. Sci. USA 92:4857-4861). The Examiner contends that Pereira et al., teach a population of isolated stromal cells that are removed from the body. Since, in the Examiner's opinion, removal from the body renders such cells "immunologically isolated," the Examiner contends that Pereira et al. teach each and every single element of the claims.

As stated previously elsewhere herein, mere removal from the body does not render isolated stromal cells "immunologically isolated" as defined by Applicants. Thus, removal from the body, without more, does not teach or suggest immunological isolation as recited in claims 37, 58-61, and 65-68. Therefore, for the reasons previously set forth elsewhere herein with regard to Cerami et al., and Carter et al., Pereira et al. does not teach "immunologically isolated" cells of the invention and the reference cannot anticipate the claims of the invention under 35 U.S.C. §102(a). Thus, the rejection of claims 37, 58-61, and 65-68, should be reconsidered and withdrawn.

Rejection of Claims 37, 38, 55, and 57-68, Under 35 U.S.C. § 103(a)

Claims 37, 38, 55, and 57-68, stand rejected under 35 U.S.C. § 103(a) as being, in the Examiner's view, unpatentable over Carter et al. (1992, Blood 79:356-364) or, alternatively, over Cerami et al. (U.S. Pat. No. 5,846,796), taken with Ala-Kokko et al. (1991, J. Biol. Chem. 266:14175-14178), Mardon et al. (1987, Cell Tissue

Res. 250:157-165), Beresford et al. (1992, J. Cell Sci. 102:341-351), and Flier (1995, Cell 80:15-18). Applicants respectfully submit that the combination of either Carter et al. or Cerami et al. with the other references (*i.e.*, Ala-Kokko et al., Mardon et al., Beresford et al., and Flier) does not render claims 37, 38, 55, and 57-68, *prima facie* obvious under 35 U.S.C. § 103(a).

The three-prong test which must be met for a reference or a combination of references to establish a *prima facie* case of obviousness has not been satisfied in the instant matter. The MPEP states, in relevant part:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. MPEP § 2142.

None of these criteria have been met here.

The Examiner contends, as discussed previously elsewhere herein, that Carter discloses a population of immunologically isolated stromal cells since Carter teaches removing the cells from the body which, according to the Examiner, removes them from the immune system and renders the cells "immunologically isolated" as defined by Applicants in the present application.

Alternatively, the Examiner contends that Cerami discloses a population of isolated mesenchymal cells comprising a gene construct operably linked to regulatory elements which function in the cells. Apparently, the Examiner continues to assert, as more fully discussed previously elsewhere herein, that the cells taught by Cerami are "immunologically isolated stromal cells" because they are removed from the body which isolates the cells from the immune system.

As more fully pointed out previously elsewhere herein, mere removal of cells from the body does not teach the "immunologically isolated" stromal cells of Applicants' invention. That is, the "immunologically isolated" stromal cells of the present invention must be transplanted into a recipient where the cells are physically

separated from the recipient's immune system. Only then are the stromal cells "immunologically isolated" as defined by Applicants. Thus, neither Cerami nor Carter teaches or suggests "immunologically isolated stromal cells" as disclosed by Applicants.

Applicants respectfully submit that combining Cerami or Carter with Ala-Kokko, Mardon, Beresford and Flier, does not correct the deficiencies of Cerami and/or Carter since none of these references, or the combination thereof, teaches or suggests "immunologically isolated" stromal cells as defined by Applicants. That is, none of the references, nor the combination of references, teaches or suggests implanting stromal cells into a recipient where the cells are physically separated from the recipient's immune system.

The Examiner does not contend that any of these references, nor the combination thereof, physically separate a transplanted cell from the immune system of the recipient. Indeed, Mardon, which is the only reference that discusses implanting a cell using microencapsulation, teaches placing stromal cells in a diffusion chamber but does not teach or suggest maintaining the cells physically separated from the recipient's immune system. More specifically, Mardon teaches using "matched donor" cells in that both the donors and recipients were syngeneic, inbred PVG/Ola rats. Mardon makes no reference whatsoever to maintaining the cells separate from the host's immune system. Indeed, there would have been no need for Mardon to maintain the cells immunologically isolated from the recipient immune system since Mardon teaches using syngeneic, matched donor cells "to minimise host immunological reaction against the implant" (Mardon at page 157, right-hand column). Further, there is no suggestion in Mardon that any proteins expressed by the implanted cells were secreted beyond the diffusion chamber. Instead, Mardon teaches using a diffusion chamber to assess the amount of bone and cartilage growth in the chamber under various *in vivo* conditions and the reference has nothing whatsoever to do with delivering a beneficial protein to a recipient. Thus, there is no teaching or suggestion in Mardon of using "immunologically isolated" stromal cells that are isolated from the recipient's immune system, to deliver a beneficial protein, and Mardon does not correct the deficiencies of Carter or Cerami.

Therefore, even assuming, *arguendo*, that the references teach as urged by the Examiner, Ala-Kokko, Mardon, Beresford and Flier, neither alone nor combined, do not teach or suggest the crucial element lacking in Cerami and/or Carter, *i.e.*, that the cells be implanted into and be physically separated from the immune system of the recipient. Thus, neither the combination of Cerami with Ala-Kokko, Mardon, Beresford and Flier, nor the combination of Carter with these references, can render the claims *prima facie* obvious under 35 U.S.C. §103(a).

In addition, there would have been no motivation to combine Cerami or Carter with Ala-Kokko, Mardon, Beresford and Flier to produce immunologically isolated stromal cells. This is because neither Cerami nor Carter, alone nor combined with the other references, teaches or suggests "immunologically isolated" stromal cells as disclosed by Applicants. Moreover, one skilled in the art would not have been motivated to combine Carter or Cerami with Ala-Kokko, Mardon, Beresford, and Flier, since none of these references, or the combination thereof, teaches or suggests using "immunologically isolated" stromal cells to deliver a beneficial protein. Therefore, because there would be no motivation to combine these references since the combination does not teach or suggest "immunologically isolated" stromal cells, the combination of Cerami or Carter with Ala-Kokko, Mardon, Beresford, and Flier, cannot render the claims *prima facie* obvious under 35 U.S.C. §103(a).

In light of the foregoing arguments, it is clear that there was no reasonable expectation of success in combining the references to produce "immunologically isolated" stromal cells to deliver a beneficial protein to the recipient of the cells. That is, a person of ordinary skill in the art would not expect to succeed in producing "immunologically isolated" stromal cells to deliver a beneficial protein to a transplant recipient by combining references that have no suggestion or teaching as to how to deliver a beneficial protein to a recipient using stromal cells where the donor and recipient are not matched to avoid immune rejection of the implant. As discussed previously elsewhere herein, Cerami and Carter do not discuss implanting cells into a recipient at all (Cerami) or implanting cells which are physically separated from the recipient's immune system (Carter). Further, Ala-Kokko, Beresford, Flier and Mardon do not teach or suggest implanting non-matched stromal cells into a recipient where the

stromal cells avoid reaction by the recipient's immune system and express a beneficial protein. Thus, there could be no reasonable expectation of success that combining Cerami or Carter with Ala-Kokko, Beresford, Flier and Mardon would result in the present invention.

For the reasons discussed above, the combination of Cerami or Carter with Ala-Kokko, Beresford, Flier and Mardon, cannot render claims 37, 38, 55, and 57-68 *prima facie* obvious under 35 U.S.C. § 103(a) and, therefore, the rejection should be reconsidered and withdrawn.

Summary

Applicants respectfully submit that each rejection of the Examiner to the claims of the present application has been either overcome or is now inapplicable, and that each of claims 37, 38, and 55-68, is in condition for allowance. Reconsideration and allowance of each of these claims are respectfully requested at the earliest possible date.

Respectfully submitted,

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(Date)

By: _____

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